Pharmacokinetic Models for Nicotine and Cotinine

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Motivation

to relate steady-state urinary cotinine levels to atmospheric nicotine concentrations:

- a simple compartmental kinetic analysis

to use cotinine as a biomarker:

- a physiologically based pharmacokinetic model PBPK

advantage from its biologically motivated structure:

- direct incorporation of biochemical data
- biologically constrained comparison of model predictions with experimental time courses

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Description

PBPK Models of Nicotine and Cotinine for Rats and Humans

for plasma kinetics of nicotine and cotinine:

- inclusion of saturable nicotine binding in the brain, heart, and lung

rat model:

- scaled to mouse and man

human model:

- inclusion of forearm compartment

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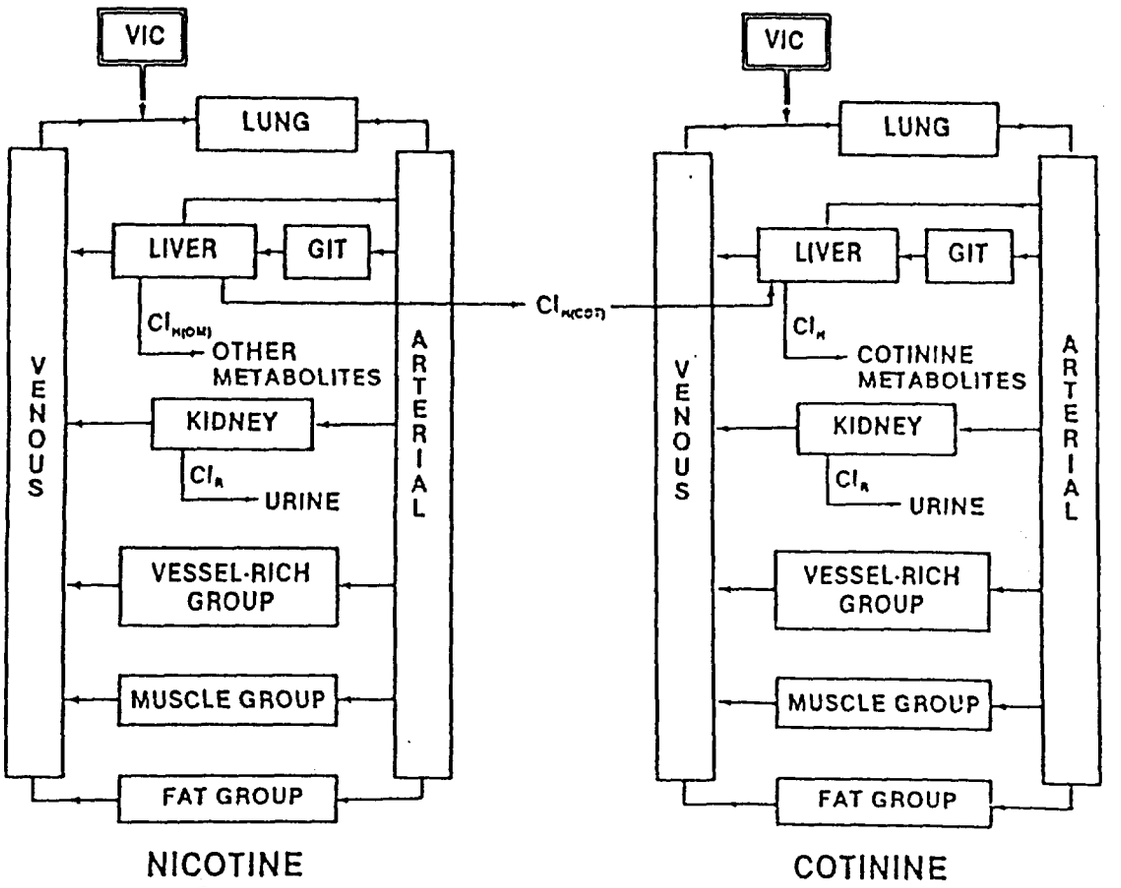

Figure 12.1 Conceptual physiologically based pharmacokinetic model for nicotine and cotinine. (From Robinson *et al.*, 1992.)

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Application

four issues related to the use of cotinine as a biomarker:

(1) contribution of dietary intake

(2) plausible upper bound for cotinine concentrations associated with ETS exposure

(3) impact of high affinity, low capacity binding in nonsmokers with low ETS exposure

(4) impact of pharmacokinetic uncertainty and variability on the inference of individual ETS exposure

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Uncertainty

two kinds:

(1) causing bias (overestimation)

- dietary intake
- nicotine binding

(2) broadening of confidence

- uncertainty in the fraction of nicotine converted to free cotinine
- rates of metabolic and urinary clearance (interindividual variability)

grouping of parameters:

- physiological (volumes and flows)
- tissue distribution (partitioning and binding)
- kinetic (absorption, metabolism, clearance)

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Physiological Parameters

(1) body weight and weights of the individual organs or tissue groups

(2) total blood flow and flows to each organ or tissue group

(3) alveolar ventilation rate

grouping of tissues: "vessel-rich"
"slowly perfused"

venous infusion compartment (forearm)

no description of: inhalation
oral exposure

not as influental as distribution and kinetic parameters

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Distributional Paramters

Tissue Partitioning

- initially steady-state tissue/blood concentration ratios then iteratively adjusted
- 2- to 5-fold difference in corresponding tissue
- lack of reproducibility

Tissue Binding (in brain, lung, heart)

- nonlinear pharmacokinetics at low concentrations:
  miscalculation of exposure for the least exposed

to date, no careful investigation of this possibility

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Kinetic Parameters

most significant parameters:

absorption, metabolism, clearance } of { nicotine, cotinine

Variation of hepatic and renal clearance values within the range of reported values:

- no exaggerated response of model structure reflects the natural interaction of
  - clearance measures
  - distribution volumes
  - elimination rates

Published human data on nicotine and cotinine infusion

variation in reported half lives	8-fold	3-fold
variation in distribution volume	6-fold	5-fold

Variability dominates even uncertainty.

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OSHA Conclusion

PBPK models are important tools for characterizing and quantifying internal doses.

OSHA seeks comment on the applicability of this approach in ascertaining the relationship between adverse health effects and exposure to ETS.

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